

<p>Institution: University of Reading</p>
<p>Unit of Assessment: 10 Mathematical Sciences</p>
<p>Title of case study: Development of novel adaptive designs to improve efficiency in clinical trials</p>
<p>Summary of the impact. Clinical trials are costly to the pharmaceutical industry and public funding bodies, require major commitment from volunteer patients and take significant time to lead to patient benefit. Adaptive designs are one approach which seeks to improve the efficiency of such studies. Statistical research at Reading has led to novel methodology for the design and analysis of clinical drug trials within the framework of adaptive designs which has the potential to reduce the time taken for effective drugs to reach the market and thus benefit specific patient groups. To date the research has had impact in three major ways: i) it has been adopted by pharmaceutical companies as a means of improving the efficiency of their clinical trials, ii) the research has been cited in the regulatory guidance on adaptive clinical trial design, and iii) it has increased awareness by clinicians and other medical professionals of the potential benefit of the adaptive design methodology to their patient groups. Hence, the research has influenced industry, regulatory and health professionals with potential significant economic benefit and improved outcome for patients.</p>
<p>2. Underpinning research.</p> <p>Traditionally the introduction of a new drug onto the market involves the implementation of a series of clinical trials, progressing through Phases I, II (sometimes split into IIa and IIb), III trials, with the studies increasing in size, duration, and thereby costs and complexity, in order to unequivocally demonstrate the efficacy and safety of a drug or drug combinations, in defined patient groups. Phase I trials are often first-in-man studies to consider safety, phase II trials are looking for evidence of efficacy (IIa trials sometimes called proof-of-concept studies, with IIb trials considering the question of finding an appropriate dose or treatment format) and phase III trials are the definitive comparison of, usually, a single experimental treatment with a control, either the current standard or placebo. These trials take many years to complete with most phase III trials for cancer treatment, for example, taking up to 8-10 years to reach conclusion.</p> <p>Conventionally the later phases of the drug development process (IIb and III) are designed as what are known as 'fixed sample size trials'. In such designs the number of patients to be recruited to the particular trial is calculated in advance of the study and data are collected on all of the patients before any analyses are carried out. This statistical approach was originally developed in the context of agricultural trials where all measurements naturally occur simultaneously at harvest. In the medical context, all observations are not available simultaneously as patients are recruited to trials sequentially over a period of months, if not years. This difference in the method of data accrual led to a different approach being proposed for use in some clinical settings – for example where patient recruitment is slow and over a long duration, combined with rapidly observable measurements – that of 'sequential trials' / 'group sequential trials'. In such a trial, data from patients are analysed at one or more interim points in the trial as they accumulate, in order to determine whether there is already sufficient evidence to draw valid conclusions about the efficacy and safety of the treatment under study. Research into this methodology peaked around the mid-to late- 1990's. Meanwhile, interest was growing in the possibility that clinical trials could be designed with other <i>adaptive</i> features (not just stopping for efficacy / futility), such as changing the patient population under study, changing the primary endpoint, changing the treatment regimens being tested. Such adaptations have significant potential to reduce the time taken for definitive results to be obtained from clinical trials and are therefore of great interest to the pharmaceutical industry in reducing the cost of drug development and to medical professionals in accelerating the availability of new treatment regimens for their patients. The over-arching term now commonly used for trials where adaptations are planned as part of their conduct is 'adaptive designs'.</p> <p>Partially funded by grants for methodological research from the pharmaceutical company, Novartis, researchers at the University of Reading were one of the first groups to begin work on developing methodology in this field. The setting envisaged was where it is desirable to take more than one experimental treatment into phase III, along with the control treatment and then to make a selection, at a first interim analysis, of the most promising of these treatments to continue in the trial along with the comparator (treatment selection). This approach might be appropriate when a stand alone phase IIb trial has not been conducted perhaps because there are only a small</p>

number of candidate doses or treatments of interest, or where the phase IIb study has been conducted but a single experimental treatment was not identified. Taking the existing 'group sequential framework', we introduced a treatment selection element into the design ([1] in Section 3). The methodological development was further progressed: i) to allow the treatment selection to be made using a different, (usually available earlier), endpoint to that which is the primary interest ([3] in Section 3), ii) with associated consideration of correlation ([2] in Section 3) and then, iii) to a consideration of how further flexibility could be introduced by allowing the treatment selection to happen over a number of successive stages, not just at the first interim stage ([4] in Section 3). Once such designs had been developed it was necessary to determine a new analysis framework since traditional methods of statistical analysis are no longer appropriate. Methodology for analysis was also developed ([5] in Section 3). Because these new designs combine the dose-finding / treatment selection element of the traditional phase II (in particular IIb) trial, along with the definitive confirmatory analysis of phase III, they have become known by several terms including seamless phase II/III (or sometimes IIb/III) clinical trials, adaptive seamless designs, adaptive group sequential designs.

The research was conducted by Dr Nigel Stallard and Dr Susan Todd (both Senior Research Fellows in the Medical and Pharmaceutical Statistics Research Unit at that time). Dr Todd (now Professor Todd) is still at the University of Reading, whereas Dr Stallard (now Professor Stallard) moved to the University of Warwick in 2005. The work described in [4] in Section 3 included a contribution by Dr Patrick Kelly who was also employed at the University of Reading as a Research Fellow at that time.

3. References to the research

1. Stallard N, Todd S (2003) Sequential designs for phase III clinical trials incorporating treatment selection. *Stat Med* 22, 689-703. DOI:10.1002/sim.1362
2. Todd S (2003) An adaptive approach to implementing bivariate group sequential clinical trial designs. *J Biopharm Stat* 13, 605-619. DOI:10.1081/BIP-120024197
3. Todd S, Stallard N (2005) A new clinical trial design combining phases 2 and 3: Sequential designs with treatment selection and a change of endpoint. *Drug Inf J* 39, 109-118. ISSN 0092-8615/2005
4. Kelly, P.J., Stallard, N. and Todd, S. (2005). An adaptive group-sequential design for phase II/III clinical trials that select a single treatment from several. *J. Biopharmaceutical Stat* 15, 641-658. DOI: 10.1081/BIP-200062857
5. Stallard N, Todd S (2005) Point estimates and confidence regions for sequential trials involving selection. *J Stat Plan Inference* 135, 402-419. DOI: 10.1016/j.jspi.2004.05.006

These five publications have received a total of 138 citations, including 68 for [1] and 26 for [3].

Grants

"Combined phase II/III clinical trial designs". Four grants totalling **£104,400** from Novartis Pharma (with Dr N. Stallard and Professor J. Whitehead, then MPS Research Unit). *January 2000 – December 2004*.

"Comparison of adaptive designs with group sequential designs when treatment selection and evaluation are required". **£20,000** from Novartis Pharma (with Dr N. Stallard, then MPS Research Unit). *September 2002 – February 2003*.

Details of the impact.

The impact of the research has taken place through three routes: i) the uptake of the methodology in the implementation of clinical trials by two pharmaceutical companies, ii) citation of the research in the regulatory guidance on adaptive clinical trial design, and iii) increased awareness by clinicians and other medical professionals of the benefit of the adaptive design methodology in their patient groups.

i) Uptake of the research by pharmaceutical companies

The underpinning research was initially disseminated through conference presentations attended by industry professionals. The full publication of the research in the statistical literature in 2003 and 2005, led to two companies independently approaching Drs Stallard and Todd to discuss the research who each subsequently adopted the phase II/III adaptive design approach proposed by the Reading team in their drug development programmes, as outlined below.

AstraZeneca:

Based on the Reading team's approach, AstraZeneca designed a phase II/III multi-national pivotal trial ([1,2] in Section 5), HORIZON III, for cediranib (Recentin). The impact of the team's work in

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this setting was illustrated in a press release ([3] in Section 5) to the investment community in February 2008, which contained a quote by John Patterson, AstraZeneca's Executive Director for Development, who said: "*Due to the Phase II/III trial design, HORIZON III is able to move directly into Phase III utilizing all the Phase II data and this saves valuable time in assessing the potential benefit of RECENTIN in the first line metastatic colorectal cancer setting*". By adopting this new methodology there is clear utility for pharmaceutical companies in terms of greater efficiency in clinical trials via potential for reducing the numbers of patients entered into trials with significant ethical benefits. The AstraZeneca development programme continues today through further clinical trials, although cediranib is not yet available in the UK.

The study by AstraZeneca was, to our knowledge, one of the first seamless phase II/III trials to be conducted by any pharmaceutical company. To date the total number of seamless phase II/III studies remains small whilst companies assess the benefits of these new approaches. The results of the completed trial have been presented by AstraZeneca at international medical conferences ([4] in Section 5) and in 2012, a presentation was given at the PSI (Statisticians in the Pharmaceutical Industry) annual conference entitled "Adaptive Trial Designs: Lessons Learned in Oncology in AstraZeneca" ([5] in Section 5). Through this outreach the concept of seamless adaptive designs as a plausible approach to clinical trial study design has been highlighted to the medical community and to industry. AstraZeneca have indicated that they would consider the adaptive design approach in future trials and have developed their own code for implementation, based on the methodological concepts described in Reading's underpinning research.

Avexa:

Avexa, an Australian company, was the second pharmaceutical company to implement a trial design based on the underpinning research in the development of apricitabine, a treatment for drug-resistant HIV ([6] in Section 5). The study, AVX301, began recruiting in February 2008 and closed recruitment in January 2010. It was stopped for reasons not associated with the trial design. Avexa press releases discuss the progress of the study, with positive reference to the adaptive trial approach ([7] in Section 5).

ii) Use in regulatory guidance on clinical trial design

Novel adaptive designs and the associated analytical frameworks, such as those developed by the team at Reading, are having an increasing impact on current thinking in clinical trial design within the pharmaceutical industry. Indeed, two key regulatory authorities have recently produced guidance documents on adaptive designs (US Food and Drug Administration (FDA), 2010; European Medical Agency, 2007); both organisations anticipate that more clinical trials will be designed using this framework and the FDA cite the Reading work ([4, 5] in Section 3) in their guidance document ([8] in Section 5). Whilst it is incorrect to state that the research undertaken at Reading was the sole catalyst for driving such change in clinical trial approach, the citation of our work in global guidelines such as these provides indication of our contribution.

iii) Increased awareness by clinicians and other medical professionals of the benefit of adaptive design methodology in their patient groups.

The Reading team developed a Continuing Professional Development course entitled "Phase II/III Clinical Trials". This was delivered at Reading in November 2006 to disseminate adaptive trial methodology in general and the research undertaken at Reading in particular. Dr Jeremy Chataway (St Mary's Hospital), a Multiple Sclerosis (MS) specialist participated in the course. Several years later, Dr Chataway contacted Dr Todd about the possibility of initiating work on adaptive designs in this therapeutic area. A colleague of Dr Chataway's, Dr Richard Nicholas was tasked with the asking the same question of the team at Warwick University (where Professor Stallard is now working). The joint Warwick-Reading team was commissioned by the Multiple Sclerosis Society to conduct further work on adaptive design methodology in the specific setting of Secondary Progressive MS. The Society funded two projects to develop a bespoke adaptive trial design that could be used for a study of MS. The results of this work have been published and presented in several conferences in 2009 ([9] in Section 5). Clinicians in the MS field are, therefore, being made more aware of adaptive designs and their advantages.

5. Sources to corroborate the impact

Sources to corroborate the AstraZeneca implementation of the phase II/III design:

1. The study is registered (mentioning the phase II/III design) at:
www.clinicaltrials.gov/ct2/show/NCT00384176?term=HORIZON+AstraZeneca&rank=3
2. A publication of the trial design is available at:

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ico.ascopubs.org/content/early/2012/09/10/JCO.2012.42.5355/suppl/DC1

The protocol (linked at the end of the abstract) cites the research ([3] in Section 3) on p31.

3. Press release: www.astrazeneca.com/Media/Press-releases/Article/20080227--AstraZeneca-Provides-Update-On-RECENTIN-Clinical-Deve
4. Medical conference presentations on the HORIZON study:
Oral presentation: Schmoll H, *et al.* "mFOLFOX6 + cediranib vs mFOLFOX6 + bevacizumab in previously untreated metastatic colorectal cancer (MCRC): a randomized, double-blind, phase II/III study (HORIZON III). *Annals of Oncology* 21 (Supplement 8): viii189–viii224, 2010. Abstract 580O. bit.ly/1ae6QZA.
Poster: Wilson D, *et al.* Application of adaptive study designs: Phase II and III results from the cediranib (CED) horizon (HZ) II and III studies. 2011 ASCO Meeting. meetinglibrary.asco.org/content/83624-102
5. Statistical conference presentation on the HORIZON study: Presentation slides available for the presentation on "Adaptive Trial Designs: Lessons Learned in Oncology in AstraZeneca"

Sources to corroborate the Avexa implementation of the phase II/III design:

6. The study is registered (mentioning the phase 2b/3 design) at: <http://www.clinicaltrials.gov/ct2/show/NCT00612898?term=AVX301&rank=2>
7. Press releases related to the study on aprictiabine are on the company's website under the tab 'News': <http://www.avexa.com.au/> Releases on Mar 24 2009 and Jun 4 2009, amongst others, discuss study AVX301

Source to corroborate the regulatory documentation:

8. FDA Guidance: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf> Lines 1928-1930 and 1996-1997 give references 4 and 5 of Section 3, respectively.

Sources to corroborate the increased awareness by clinicians and other medical professionals

9. Conference abstracts:
"Developing a new trial design in secondary progressive multiple sclerosis: A seamless adaptive approach." Presented at: ABN Joint Annual Meeting/Spanish Society of Neurology, Liverpool, UK, Jun 22-26 2009. DOI:10.1136/jnnp.2009.195214r.
"Adaptive seamless trial designs in neurology: a case study in secondary progressive multiple sclerosis." Presented at the 19th World Congress of Neurology, Bangkok, Thailand, Oct 24-30 2009. DOI:10.1016/S0022-510X(09)70456-3.
"Adaptive clinical trials incorporating treatment selection and evaluation: methodology and application in progressive multiple sclerosis." Presented at the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Dusseldorf, Germany, Sep 09-12 2009.